The Frontiers of Organic Chemistry at the Bürgenstock Conference

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Figure 1. Klaus Müller, long-serving member of the organizing committee.

Bürgenstock: This prestigious but somewhat mysterious meeting on stereochemistry high in the Swiss alps. I had heard much about it: that it has a long tradition and very strict rules, that attendance is limited, that you do not know who is coming, let alone who is speaking, and that the speakers lecture here only once during their career. Finally, I got my chance to attend this year and I was greatly looking forward to it.

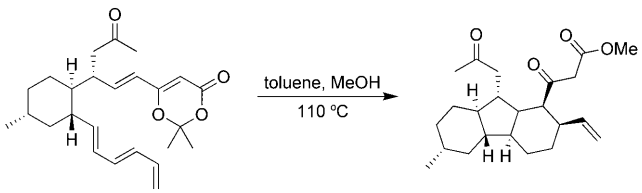
On May 17, the participants gathered for the meeting in Brunnen, not high in the alps but down at the shores of the Vierwaldstättersee; a beautiful location that will also serve as the venue for next year's meeting. Upon arrival, everyone quickly checked the program to finally discover who would be speaking, and indeed the program promised much.

The meeting started with a dinner, during which this year's president, Ben L. Feringa (University of Groningen) gave his opening address from the balcony to welcome everyone, and in particular this year's guest of honor, Dr. Klaus Müller (Figure 1), who until last year served as a member of the organizing committee. Then it was time for the conference to start, and from Sunday until Friday, the participants were treated to science of the highest level. Reflecting the broad interests of the organizing committee and the president, a very large part of organic chemistry and related disciplines was covered in the program. A few general themes could be discerned: organic synthesis and catalysis, chemical biology, and chirality. However, not all lectures can be categorized so easily, and some actually spanned more than one topic. It is impossible to capture all the exciting chemistry that was discussed in such a small report, but some snapshots are provided below.

Organic Synthesis and Catalysis

Stereochemistry inevitably plays a key role in the total synthesis of natural products, and the kick-off for the meeting was given by Ian Paterson (Cambridge). Introduced as a "master of aldol", he talked about progress in the stereocontrolled synthesis of polyketides, such as dictyostatin, and current approaches to spirastrellolide A.[1] Obviously the aldol reaction played a prominent role.

The topic of total synthesis was continued on the final day by Erik J. Sorensen (Princeton University), the co-author of Classics in Total Synthesis.[2a] His lecture started with a historical perspective by showing some classics in total synthesis, such as Robinson's synthesis of tropinone, Woodward's synthesis of chlorophyll, and Eschenmoser's synthesis of vitamin B_{12}. He then moved on to present some of his own work, which underlines that classic organic transformations, such as the Michael reaction and in particular the Diels–Alder reaction, are still very powerful tools in the synthesis of complex molecules. This point was convincingly demonstrated with the total synthesis of FR 182871, Abyssomycin C, and recent work towards the hirsutellones (Scheme 1), which involved an elegant intramolecular tandem ketene-trapping/Diels–Alder sequence.[2b]



Scheme 1. The key tandem ketene-trapping/Diels–Alder cyclization in the synthesis of the decahydrofluorenene core of the hirsutellones.[2b]

Catalysis played a very prominent role in the program: four contributions each focused on different aspects. Lawrence Que, Jr. (University of Minnesota) showed how the study of metalloenzyme mechanisms by using synthetic model complexes, and in particular non-heme iron complexes, has given rise to new bioinspired catalysts capable of stereoselective oxidation of organic substrates.[3] The role of acetic acid in non-heme iron-catalyzed oxidation reactions was also briefly discussed, which directly linked to the talk by M. Christina White later. In the second part of Que's talk, the focus was on models for α-ketoglutarate-dependent enzymes. Using the iron complex [Fe(L)(BF)] (L = hydrotris(3,5-diphenylpyrazol-1-yl)borate, BF = benzoyl formate), a high-valent $Fe^{IV}O$ intermediate

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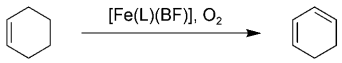
could be generated that could be intercepted by an organic substrate, such as cyclohexene, resulting in dehydrogenation and formation of cyclohexadiene (Scheme 2). Interestingly, the efficiency of the



Scheme 2. Dehydrogenation of cyclohexene by [Fe(L)(BF)]/O_2.

reaction proved not to be related to the strength of the C–H bond, but to the shape of the molecule, which has to fit in the cavity provided by the catalyst (Figure 2).[4] That is why hydrogen abstraction occurred efficiently with cyclohexene but not with ethylbenzene, even though they posses C–H bonds of similar strength.

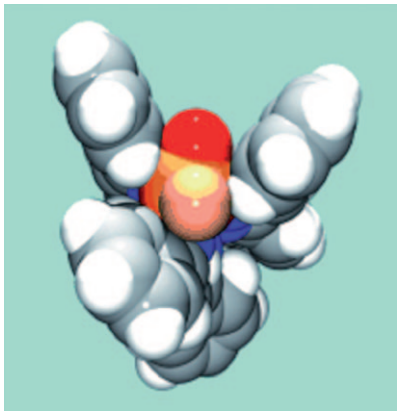


Figure 2. Space-filling model of the shape-selective cleft in the putative $Fe^{IV}O$ oxidant.[4]

M. Christina White (University of Illinois, Urbana-Champaign) impressively demonstrated in her lecture how these non-heme iron complexes can be used to streamline organic synthesis by late-stage oxidation of tertiary carbon centers. The key discovery was an iron complex of a bispyrrolidine ligand, which, in combination with acetic acid, proved to be an excellent catalyst for stereoselective hydroxylation of tertiary carbon atoms.[5] She then showed how regioselectivity can be achieved by electronic, steric, and directing effects. In the second part of the lecture, the focus was on palladium catalysis, and in particular allylic functionalization by C–H oxidation. In her lecture, White convincingly made clear that with these new catalytic methods at hand, the C–H moiety should be considered a convenient functional group in organic synthesis.

Catalysis via cationic intermediates was the topic of the lecture from F. Dean Toste (University of California, Berkeley). Of course, the focus was on gold(I) complexes, which is one of the exciting new fields in catalysis in which the Toste group plays a leading role. In addition to the synthetic applications of gold(I), an in-depth discussion of the backgrounds of the electrophilicity and reactivity of gold(I) complexes, the nature of gold-stabilized carbenes, and the importance of relativistic effects was presented.[6]

A very different perspective on catalysis was provided by Alan Rowan (Radboud University, Nijmegen), who focused on the role of motion in catalysis. In his research on processive catalysts, which are capable of epoxidizing all double bonds in polybutadiene, a key step is the threading of the polymer through the cavity of the catalyst. Rowan showed that a preassociation between the polymer and the outside of the cavity triggers the threading process by looping the polymer end into the cavity. This process causes accelerated unidirectional threading, which is reminiscent of translocation of proteins through membrane pores.[7] In the second part of his talk, he discussed single-molecule studies of enzymatic activity. It was postulated that enzymes are only active during a small fraction of time, and for the rest they are dormant, which is proposed to be related to structural dynamics and conformational changes.[8]

Chemical Biology

As was the case in previous years, the topic of chemical biology was also well-represented. Having heard about chemical synthesis of polyketides by Paterson in the first lecture, Chaitan Khosla (Stanford) showed how nature makes these highly complex structures using polyketide synthases (PKS), which are modular assembly-line enzymes. An important goal in PKS research is the construction of hybrid systems that can be used to achieve the biosynthesis of novel polyketides. Khosla presented a small catalytic module from 6-deoxyerythronolide B synthase, which is arguably the most-studied PKS. This study provided insight into the catalytic efficiency and specificity of PKS modules.[9]

The power of ribosomal synthesis was demonstrated by Hiroaki Suga (University of Tokyo), who uses a genetic reprogramming approach to form novel peptidic structures. A central role is played by "flexizyme", a versatile ribozyme that can efficiently charge tRNA with many amino acids and derivatives thereof.[10] Using a cell-free translation system many non-standard peptides and peptoids that incorporate multiple non-proteinogenic residues could be made.[11]

In his contribution, Dirk Trauner (LMU München) introduced his research on "chemical neurology". An important topic of this research is controlling neural activity with molecular switches.

The glutamate receptor can be light-gated with a so-called MAG switch, which comprises a maleimide moiety for conjugation to a cysteine, a photoisomerizable azobenzene moiety, and a glutamate analogue that acts as an agonist. It was particularly intriguing that this technology can be used in vivo to modulate the touch-evoked escape response in transgenic zebra fish larva.[12]

Xiaoliang Sunney Xie (Harvard University) presented some of his work on single-molecule spectroscopy on living systems. After an explanation of the technique, he demonstrated its power by the study of gene expression. Typically, events associated with gene expression are difficult to study because it concerns "life at low copy numbers". However, this point makes it an ideal object of study for single-molecule spectroscopy. As an example he showed how, and how fast, transcription factors, such as the *lac* repressor, find their target DNA sequence.[13]

Chirality

Unsurprisingly, considering the general theme of the conference and the interests of this year's president, a significant part of the program was devoted to chirality. Both Joanna Aizenberg (Harvard University) and Karl-Heinz Ernst (EMPA, Dübendorf, Switzerland) discussed chirality in relation to surfaces. The Aizenberg group has long been interested in crystal engineering, nanofabrication, and chiral nanostructures. After a discussion about biomineralization and how this can be controlled by using self-assembled monolayers, she impressed the audience with many pictures of beautiful chiral structures. Starting from periodic arrays of nanopillars, the capillary forces associated with the menisci cause the pillars to deform and adhere to each other after they are immersed in a liquid that is evaporated, resulting in beautiful helical assemblies (Figure 3).[14]

Supramolecular and single-molecule surface chirality was discussed by Ernst. In a recent development, his group has worked on monolayers of buckybowls (corranulenes) on Cu(111) surfaces. He showed that upon cooling, a phase transition occurs, which was attributed to the fact that cooling slows the vibrations in the molecules, which thus needs less space.[15]

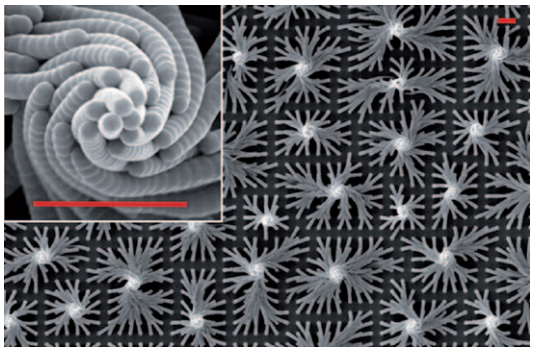


Figure 3. SEM image showing self-organized helical assemblies of nanopillars.[14] Reprinted with permission from AAAS.

A special event was organized on Tuesday afternoon: a session on "chirality and the origin of life", with contributions from Bernard Kaptein (DSM Research), Günter von Kiedrowski (University of Bonn), Meir Lahav (Weizmann Institute of Science), and Stephen Mann (University of Bristol). Although fundamental questions about both the emergence of chirality and the origin of life were not answered in this session, in his contribution, which was probably the shortest ever at a Bürgenstock meeting, Jay Siegel (University of Zürich) concluded that if "research, or the way we do the research (on this topic), changes the way we think about a problem, then we did our duty".

Two speakers who do not fit into the categories given above are Nadrian C. Seeman (New York University) and Rustem F. Ismagilov (University of Chicago). Introduced as "the world champion of DNA technology", Seeman explained the concepts of building with DNA and how this has evolved from building Holliday junctions to building three-dimensional shapes, such as cubes, and even to functional DNA devices, such as DNA walkers.[16]

The effect of space in chemical systems was described by Rustem Ismagilov. In this research, microfluidics is an important tool, as it allows spatial organization of the components of a chemical system in a highly defined fashion. Many intriguing examples of the effect of space were presented. For example, it was shown that artificial microbial communities, which are normally unstable in the lab, can be stabilized by spatially separating them in a defined way but still allowing chemical communication.[17] Starting from his work on blood clotting, he showed how bacteria can activate clotting by quorum acting. This led to the question as to whether confinement can also activate quorum sensing. In a very elegant study, Ismagilov demonstrated that quorum sensing could still be induced after confining individual cells to a small space.[18] Therefore, the conclusion was that "one is a quorum"; that is, quorum sensing is not always a collective action.

In addition to these excellent lectures, two very lively poster sessions were also held. These were preceded by a selection of "poster appetizer" talks. In general, as is intended, the program was arranged to allow much time for discussion.

Although stereochemistry is still the leading theme, and all speakers tried to incorporate some stereochemistry in their presentations, it was clear that the Bürgenstock meeting has become much more than a meeting on stereochemistry; it has

evolved to become a meeting on the frontiers of organic chemistry in the broadest sense. Overall it can be concluded that this year's Bürgenstock conference delivered on its promise and that it successfully continued the long tradition of excellence for which this meeting is famous. Ben Feringa, the president of the meeting who unsuccessfully tried to conceal the fact that it was his birthday halfway through the meeting (Figure 4),

Figure 4. Conference president Ben Feringa cutting his birthday cake.

and the organizing committee, can be congratulated on the great success of this conference. For me, the Bürgenstock conference was wonderful experience that I can highly recommend to anyone with in interest in discovering the frontiers of science.

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